PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL2005/000480	05.05.2005	05.05.2004

International Patent Classification (IPC) or both national classification and IPC
A61K31/427, A61P1/00

Applicant
RENOPHARM LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☐ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL2005/000480

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

1. Section III

1.1 Claims 1-4 and 10-64 are directed to a method of treatment of the human/animal body by therapy. Such subject-matter is considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT, and therefore no opinion shall be formulated with respect to industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT). However an opinion shall be formulated with respect to novelty and inventive step based on the alleged effects of the compounds/compositions.

1.2 Claims 1-18 are neither supported in the sense of Art 6 nor disclosed in the sense of Art 5 PCT. All the examples contained in the description refer to a particular class of compounds, namely the derivatives of thiazole as claimed in present claim 19. Nothing in the whole description allows the conclusion that what is observed with these compounds can be extended to all the members of the functional classes defined in the mentioned claims, i.e. nothing supports the notion that the treatment of irritable bowel disease can be achieved by any compound falling under the given functional definitions independently of its structure. Consequently only the class of compounds defined in claim 19 as exemplified in the examples has been searched. The present examination is also limited to this subject-matter, since no examination can be carried out in the absence of a corresponding search report.

1.3 Further to this, the coupling of the thiazole ring to a further bioactive agent residue is also not disclosed in the present application. In the description (cf. p. 20, § 5) US Provisional Patent Application 60/651,619 is "incorporated by reference" and is said to disclose such coupling. However it appears that this document has not yet been made available to the public and therefore the reference to it does not constitute a disclosure of the coupling. It follows that also the subject-matter of claims 19 in part and claims 20-28 and 44-63 entirely is not sufficiently disclosed in the sense of Art 5 PCT. The same consequences as under item 1.2 apply.

2. Section V

2.1 Cited Documents

The following documents (D) are referred to in this Opinion; the numbering will be adhered to in the rest of the procedure:

D1: WO 01/49275 A (QUEEN'S UNIVERSITY AT KINGSTON; THATCHER,

GREGORY, R., J; BENNETT, BRI) 12 July 2001

D2: US-B1-6 310 052 (THATCHER GREGORY R. J ET AL) 30 October 2001

D3: CAVICCHI M ET AL: "Inhibition of inducible nitric oxide synthase in the human intestinal epithelial cell line, DLD-1, by the inducers of heme oxygenase 1, bismuth salts, heme, and nitric oxide donors" GUT, vol. 47, no. 6, 2000, pages 771-778, XP009052245

D4: SALAS AZUCENA ET AL: "Nitric oxide supplementation ameliorates dextran sulfate sodium-induced colitis in mice" LABORATORY INVESTIGATION, vol. 82, no. 5, 2002, pages 597-607, XP001207172

D5: UEDA SHIGEO ET AL: "Structure-activity relationships of 2-aminothiazole derivatives as inducible nitric oxide synthase inhibitor." CHEMICAL & PHARMACEUTICAL BULLETIN, vol. 52, no. 5, 2004, pages 634-637, XP009052204

Unless otherwise indicated reference is hereafter made to the passages cited in the Search Report.

2.2 The prior art

WO 01/49275 A: The document discloses one compound being an NO donor based on a thiazole nucleus. The compound is used in pharmaceutical compositions for the treatment of pain (further medical use).

US 6 310 052 B1: The document discloses two compounds being NO donors based on a thiazole nucleus. The compounds are used in pharmaceutical compositions for the treatment of cerebral damage (further medical use).

XP009052245: The document establishes a potential link between NO donors and the development, and therefore the treatment, of irritable bowel disease.

XP001207172: The document establishes a clear link between irritable bowel disease and the administration of NO-donating compounds. This is shown by administration of DETA/NO

XP009052204: The document discloses the requirements for the thiazole ring to have inhibitory activity on iNOS. Required is a free 2-amino group and the absence of bulky or hydrophilic substituents.

2.3 Art 33(2) PCT (Novelty)

The subject-matter of claims 19, 29-43 and 64 of the present application meets the requirements of Article 33(2) PCT.

None of the cited documents discloses compounds based on the thiazole ring with a substituent other than hydrogen in the 2-position and having the described Y substituent, nor their medical use.

2.4 Art 33(3) PCT (Inventive step)

The subject-matter of claims 19, 29-43 and 64 of the present application does not meet the requirements of Article 33(3) PCT.

On p. 110, § 1 of the present application it is stated that "an aryl/heteroaryl group attached (at position 2) of the thiazole ring may be required for effective activity". Since not all the compounds falling under the scope of the general structure of claim 19 possess this feature it is concluded that not all of them solve the technical problem of providing new compounds for the treatment of IBD. Under these circumstances no inventive step can be acknowledged.

2.5 Art 33(4) PCT (Industrial applicability)

As stated above, no opinion is given on the question of whether present claims 1-4 and 10-64 are industrially applicable since their patentability is *inter alia* dependent upon their formulation as well as upon national and regional laws and no unifying criteria is provided in this field by the PCT.

3. Section VI

Other cited documents (Rule 70.10 PCT)

Patent number	Filing date	Priority date	Publication date
US2005/137191	17.09.2004		23.06.2005

The document discloses a number of thiazole derivatives as NO-donors for the treatment of inter alia ulcerative colitis and Crohn's disease, the two forms of IBD.